28. (AMENDED) The method of claim 21 wherein said cell is part of a tissue or organ and the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer is covalently bonded to the nuclear cell through a unit derived from reaction of a cyanuric chloride linking group on the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer to the cell surface.

a4

31. (AMENDED) [A non-immunogenic cell produced by the method of claim 21] The cellular composition of claim 2 wherein said cell is a platelet and the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer is covalently bonded to the nuclear cell through a unit derived from reaction of a cyanuric chloride linking group on the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer to the cell surface.

a5

SUMMARY OF THE OFFICE ACTION

1) Claims 1-26, 28 and 31 are under Examination
2) Claims 14 and 31 have been objected to under 37 CFR 1.75© as being improperly dependent by not limiting the subject matter of a previous claim.

3) Claims 2-7, 9, 18-19, 23-25, 28 and 31 have been rejected under the Judicially Created Doctrine of Obviousness-Type Double patenting.

4) Claims 15, 17-23, 28 and 31 have been rejected under 35 U.S.C. 112, second paragraph because of the ambiguity presented by the terms "anuclear" and "nuclear" in the claims.

5) Claims 2-7, 18-21, 23-25, 28 and 31 have been rejected under 35 U.S.C. 102(e) as anticipated by Desai et al. (U.S. Patent No. 5,578,442).

6) Claims 1, 4-5, 7-8, 10-16, 4 and 26 have been rejected under 35 U.S.C. 102(b) as anticipated by Francis et al. (WO 95/06058).

7) Claims 1, 4-5, 14-16, 24 and 16 have been rejected under 35 U.S.C. 102(a) as anticipated by Jeong et al.

8) Claims 1-16, 28 and 31 have been rejected under 35 U.S.C. 103(a) as obvious over the combination of Desai et al. in view of Francis et al.

RESPONSE TO THE OBJECTIONS AND REJECTIONS

1) Claims 1-26, 28 and 31 are under Examination

Applicants confirm their election, have cancelled the majority of the non-elected claims, and authorize the examiner to cancel any remaining non-elected claims upon allowance of the elected claims in order to provide a Notice of Allowance and Issue Fee Due.

2) Claims 14 and 31 have been objected to under 37 CFR 1.75 (c) as being improperly dependent by not limiting the subject matter of a previous claim.

Applicants have amended claims 14 and 31 to overcome this objection, which is now moot.

3) Claims 2-7, 9, 18-19, 23-25, 28 and 31 have been rejected under the Judicially Created Doctrine of Obviousness-Type Double patenting.

Applicants, through their attorney of record, have provided herewith a Terminal Disclaimer to overcome this rejection. This rejection is now moot.

4) Claims 15, 17-23, 28 and 31 have been rejected under 35 U.S.C. 112, second paragraph because of the ambiguity presented by the terms "anuclear" and "nuclear" in the claims.

Claims 15, 17-23, 28 and 31 have been amended to remove this ambiguity. The issue of this rejection is now moot.

5) Claims 2-7, 18-21, 23-25, 28 and 31 have been rejected under 35 U.S.C. 102(e) as anticipated by Desai et al. (U.S. Patent No. 5,578,442).

The Claims (represented by Claim 1, which is also highlighted for emphasis, below) specifically recite that the composition includes:

8. A non-aggregating, non-immunogenic anuclear cellular composition comprising:

a) a mammalian anuclear cell having a cell surface and antigenic determinants on said surface;

a sufficient amount of hydrophilic, biocompatible, non-immunogenicity providing compound or polymer **covalently attached** to said surface so that recognition of said antigenic determinants on said surface is blocked by said covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer. (Emphasis added).

These recitations are absolute and clear limitations on every claim remaining in the application. That specific limitation must be taught by Desai et al. for this rejection to be tenable. Desai et al do not teach covalent bonding of a non-immunogenic compound on a virus particle surface.

There is no specific disclosure which has been cited in the Office Action which asserts that the linker molecule is covalently bonded to the virus particle. The disclosure of Desai et al. clearly shows both the limitation of "covalent bonding" and bonding to a "virus particle" limitation to be absent from the invention contemplated by Desai et al.

Absence of Covalent Bonding

On column 5, line 38 through column 6, line 60, Desai et al. clearly describe a method and composition which "associates" a polycationic species with the negatively charged cell surface (e.g., column 5, lines 55-60). The language and disclosure in this section clearly denotes and describes an ionic association of the polycationic composition which renders the cells non--immunogenic, Desai et al. repeatedly use language and description consistent with only ionic associations and inconsistent with covalent bonding. Even the reaction mechanisms for removal of the polycation binding to the cells and tissue is clearly incapable of relating to covalent bonding. Note specifically column 5, lines 55-67. The anions used to remove the polycationic materials from the cell

surfaces must have high ionic strength. To remove a material from the cell surface which had been covalently bonded, specific types of chemical activity would have to be described.

The same section also refers to the necessary concentration of anionic species to reverse polycation binding to cells or tissue (column 5, lines 61-67). This language is specifically consistent with the existence of ionic binding and is inconsistent with covalent bonding. The fact that there is never any disclosure of specific reactive groups and reactions between the linker molecule and the cell surface is a further indication of the absence of any teaching or disclosure of covalent bonding to the cell surface by the linker molecule. In the absence of any indication of the necessary groups and reaction conditions for covalent bonding, and the consistent reference to ionic associations and ionic methods of release, it is absolutely clear that Desai et al. do not teach covalent bonding of the linker molecule to the cell surface.

Desai et al. can not sustain a rejection under 35 U.S.C. 102(e) against the claims. The reference does not teach covalent bonding of the linker molecule to the virus particle surface or even to a cell surface. Although the Office Action repeats its assertion of the inherent formation of covalent bonds with the surfaces of cells or tissues, these assertion do not survive any serious scientific evaluation of the underlying technology.

The evidence to the contrary is that if the listed acids were capable of inherently forming covalent bonds with cells and tissues (in the absence of enzymes or catalysts for that specific reaction), life as we know it would cease on the Earth. If these and the other available alpha-amino acids could covalently bond to cells and tissues without enzymatic activity (which is not present in the *in vitro* environment of Desai), the cells and tissues within the body would bond together. This would mean that blood cells would bond to vascular walls (e.g., cause clots and strokes), would crosslink tissue (e.g., the lungs), and cause other undesirable activities within the human body. These acids are present in foods, supplements and by-products of digestion and would covalently bond to the surface of the stomach, intestines, and other organs.

In summary, there appears to be clear evidence that the listed polyamino acids do not spontaneously, within the environment presented by Desai, form covalent bonds with cells and tissues.

6) Claims 1, 4-5, 7-8, 10-16, 4 and 26 have been rejected under 35 U.S.C. 102(b) as anticipated by Francis et al. (WO 95/06058).

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al. in view of Francis et al. (WO 95/06058). This rejection is also respectfully traversed. Although Francis does apparently incidentally show the covalent bonding of a moiety (including PEG, the erythrocytes of Example 7) to the surface of a red blood cell, the bonding is done for the purpose of differentiating cells (so that they may be separated by ionic or electrostatic or other physical process), and only mammalian cells, as opposed to virus particles are bonded with the differentiating compound.

This rejection therefore fails because the combination of references fails to provide any motivation for the covalent bonding of compounds to the surface of nuclear or anuclear cells **with the provision of an anti-immunogenic effect**. Even with the teaching of Francis that compounds can be covalently bonded to mammalian cells (including red blood cells in Example 7), the specification specifically replicated the process of Francis et al., compared those cells to cells produced according to the present invention, and clearly established that the process of Francis et al. (**which was not intended to provide an anti-immunogenic** effect) did not produce an anti-immunogenic effect. In this regard, please note Example IX, and especially the conclusion on Page 30, lines 15-29, especially where it is stated in lines 25-29 that:

> "**As shown, CmPEG readily modifies the RBC** [red blood cell] **surface and confers immunocamoflage. In contrast, the TmPEG method as taught by Francis fails to significantly modify RBC and does not yield any protection from immune recognition (Figure 1).** (*emphasis added*)

All of the claims, in various language, effectively recited "A non-aggregating, non-immunogenic ... cellular composition..." Francis et al. has been shown to provide a cell composition that is **NOT** non-immunogenic. Francis et al. has therefore been shown to fail to anticipate the present invention. As direct, detailed, and uncontraverted evidence has been provided that shows that Francis et al. fails to anticipate this critical language of the claims, the rejection is clearly in error and must be withdrawn.

There is no motivation to perform a non-immunizing activity on nuclear or anuclear cells and clear evidence that the process of Francis et al. cannot provide that activity. Without such ability or motivation, there is no underlying basis for the assertion of obviousness.

7) Claims 1, 4-5, 14-16, 24 and 16 have been rejected under 35 U.S.C. 102(a) as anticipated by Jeong et al.

Applicants provide herewith an official correspondence from Marcel Dekker clearly identifying the publication date of the Jeong et al. article. The evidence clearly shows that the actual publication date of the reference is after the priority date of this application. The rejection therefore fails to meet the statutory requirements as a reference under 35 U.S.C. 102(a). The present application has been provided with a priority date under 35 U.S.C. 120 of June 27, 1996 (from U.S. Patent No. 5,908,624), the Examiner has acknowledged subject matter priority through the obviousness-type double patenting rejection, and the priority date is even before the publication date of Jeong et al., and not merely within on year of the publication date. This rejection is in error as a matter of law.

8) Claims 1-16, 28 and 31 have been rejected under 35 U.S.C. 103(a) as obvious over the combination of Desai et al. in view of Francis et al.

This rejection is clearly in error, at least for the following reason. Desai et al. has been clearly established as failing to show covalent bonding of PEG to cell surfaces. The Francis et al. reference, showing a specific format for providing covalent bonding of PEG to a cell surface for a purpose other than providing non-immunogenicity, **fails to provide non-immunogenicity by his sole described method.** That fact has been established by direct comparison of the Francis et al. method and a method according to the practice of the invention. Therefore, even if the methods of Desai et al. and Francis et al. were combined, they would not be expected to provide the properties recited in the claims.

The rejection is therefore clearly in error. Not only was the covalent bonding shown by Francis et al. not intended to provide non-immunogenicity, the actual effect of the process failed to provide non-immunogenicity. The combination therefore fails to show that the invention as a whole, including the resulting properties, are obvious. The rejection therefore fails to meet minimum statutory requirements to establish a *prima facie* case of obviousness. The rejection is in error and must be withdrawn.

Additionally, the purpose for the covalent bonding of compounds to mammalian cell shown by Francis is for a fundamentally different purpose than that shown by Desai. Desai requires the preparation of reversible, non-adhesive cells, while Francis is teaching the preparation of adducts of a polymer and a targeted material, which are shown to be differentiable (e.g., in solvents so that they separate). Although Desai does teach that his reversible attachment (ionic attachment) of can reduce aggregation, Francis appears to indicate that aggregation still occurs with both his inventive composition and with control compositions (Examples 3 and 4). There is no nexus between the two references that would allow their combination, even if they are proposed to be combined. In addition, with this fundamental difference in the objective of the two references, they would not be combined to motivate one skilled in the art to modify the surface of a viral particle, a process not taught in either reference.

This rejection is in error and must be withdrawn.

Authorization is hereby given to charge any additional fees or credit any overpayments that may be deemed necessary to Deposit Account Number 50-1391.

Respectfully submitted,

MARK D. SCOTT et al.

By their Representatives,

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Date: July 10, 2001

By: _____
Mark A. Litman
Reg. No. 26,390

CERTIFICATE UNDER 37 C.F.R. 1.8: The undersigned hereby certifies that this Letter is being deposited in the United States Postal Service, as first class mail, with sufficient postage, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on July 10, 2001.

Mark A. Litman
Name

_____
Signature

CLEAN COPY OF AMENDED CLAIMS REQUIRED UNDER 37 C.F.R. 1.121

1. A non-aggregating, non-immunogenic anuclear cellular composition consisting of:

a) a mammalian anuclear cell having a cell surface and antigenic determinants on said surface;

b) a sufficient amount of hydrophilic, biocompatible, non-immunogenicity providing compound or polymer covalently attached to said surface so that recognition of said antigenic determinants on said surface is blocked by said covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer.

2. A non-aggregating, non-immunogenic nuclear cellular composition in which at least 25% by number of nuclear cells in said composition remain viable for 96 hours consisting of:

a) a mammalian nuclear cell having a cell surface and antigenic determinants on said surface;

b) a sufficient amount of hydrophilic, biocompatible, non-immunogenicity providing compound or polymer covalently attached to said surface so that recognition of said antigenic determinants on said surface is blocked by said covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer.

3. A non-aggregating, non-immunogenic nuclear cellular composition having insufficient amounts of toxic materials within said composition to be toxic to nuclear cells within said composition consisting essentially of:

    a) a mammalian nuclear cell having a cell surface and antigenic determinants on said surface;

    b) a sufficient amount of hydrophilic, biocompatible, non-immunogenicity providing compound or polymer covalently attached to said surface so that recognition of said antigenic determinants on said surface is blocked by said covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer.

4. A non-aggregating, non-immunogenic anuclear or nuclear cellular composition consisting of:

    a) a mammalian anuclear or nuclear cell having a cell surface and antigenic determinants on said surface;

    b) a sufficient amount of hydrophilic, biocompatible, non-immunogenicity providing compound or polymer covalently attached to said surface so that recognition of said antigenic determinants on said anuclear or nuclear cell surface is blocked by said covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer, said composition being free of any by=products from the covalent attachment of said hydrophilic, biocompatible, non-

immunogenicity providing compound or polymer to said anuclear or nuclear cell surface.

5. A non-aggregating, non-immunogenic cellular composition having insufficient amounts of toxic materials within said composition to be toxic to cells within said composition consisting essentially of:
    a) a mammalian nuclear cell having a cell surface and antigenic determinants on said surface;
    b) a sufficient amount of hydrophilic, biocompatible, non-immunogenicity providing compound or polymer covalently attached to said surface so that recognition of said antigenic determinants on said surface is blocked by said covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer.

6. A viable, non-aggregating, non-immunogenic cellular composition consisting essentially of:
    a) a mammalian nuclear cell having a cell surface and antigenic determinants on said surface;
    b) a sufficient amount of hydrophilic, biocompatible, non-immunogenicity providing compound or polymer covalently attached to said surface so that recognition of said antigenic determinants on said surface is blocked by said covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer.

7. A non-immunogenic cellular composition consisting essentially of:

a) a mammalian nuclear cell having a cell surface and antigenic determinants on said surface;

a sufficient amount of hydrophilic, biocompatible, non-immunogenicity providing compound or polymer covalently attached to said surface so that recognition of said antigenic determinants on said surface is blocked by said covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer.

14. The cellular composition of claim 1 wherein said cell is anuclear cell and the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer is covalently bonded to the nuclear cell through a unit derived from reaction of a cyanuric chloride linking group on the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer to the cell surface.

15. The cellular composition of claim 1 wherein said anuclear cell is a red blood cell.

17. The cellular composition of claim 1 wherein said anuclear cell is a platelet.

18. The cellular composition of claim 2 wherein said cell is a lymphocyte and the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer is covalently bonded to the nuclear cell through a unit derived from reaction of a cyanuric chloride linking group on the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer to the cell surface.

19. The cellular composition of claim 2 wherein said linking moieties are covalently attached to said antigenic determinants on said cell surface and said nucleated cell is a vascular endothelial cell.

20. The cellular composition of claim 2 wherein said linking moieties are covalently attached to said antigenic determinants on said cell surface and said nucleated cell is a hepatic cell.

21. The cellular composition of claim 2 wherein said linking moieties are covalently attached to said antigenic determinants on said cell surface and said nucleated cell is a neuronal cell.

22. The cellular composition of claim 2 wherein said linking moieties are covalently attached to said antigenic determinants on said cell surface and said nucleated cell is a pancreatic cell.

23. The cellular composition of claim 2 wherein said linking moieties are covalently attached to said antigenic determinants on said cell surface and said nucleated cell is an epithelial cell.

28. The method of claim 21 wherein said cell is part of a tissue or organ and the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer is covalently bonded to the nuclear cell through a unit derived from reaction of a cyanuric chloride linking group on the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer to the cell surface.

31. The cellular composition of claim 2 wherein said cell is a lymphocyte and the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer is covalently bonded to the nuclear cell through a unit derived from reaction of a cyanuric chloride linking group on the covalently bonded hydrophilic, biocompatible, non-immunogenicity providing compound or polymer to the cell surface.